Dexamethasone minimizes the risk of cranial nerve injury during CEA

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Objective: **The incidence of cranial and cervical nerve injury during carotid endarterectomy (CEA) ranges from less than 7.6% to more than 50%. Lesions are mainly due to surgical maneuvers such as traction, compression, tissue electrocoagulation, clamping, and extensive dissections. The use of dexamethasone (DEX) and its beneficial effects in spinal cord injuries have already been described. We investigated whether DEX could also be beneficial to minimize the incidence of cranial and cervical nerve injury during CEA.**

Purpose: **To evaluate whether dexamethasone is able to reduce the incidence of cranial nerve injuries.**

Materials and Methods: **From March 1999 through April 2006, 1126 patients undergoing CEA because of high-grade carotid stenosis were enrolled and randomized by predetermined randomization tables into two groups. The first group, "A", included 586 patients that all received an intravenous administration of dexamethasone following a therapeutic scheme. The second group, "B", included 540 control subjects that received the standard pre- and postoperative therapy. All patients were submitted to a deep cervical plexus block, eversion carotid endarterectomy, and selective shunting. Three days after the operation, an independent neurologist and otorhinolaryngologist evaluated the presence of cranial nerve deficits. All patients (group A and group B) showing nerve injuries continued the treatment (8 mg of dexamethasone once in the morning) for 7 days and were re-evaluated after 2 weeks, 30 days, and every 3 months for 1 year. Recovery time took from 2 weeks to 12 months, with a mean time of 3.6 months. The χ^2 test was used to compare the two groups and to check for statistical significance.**

Results: **The incidence of cranial nerve dysfunction was higher in group B and the statistical analysis showed a significant effect of dexamethasone in preventing the neurological damage ($P = .0081$). The incidence of temporary lesions was lower in group A and the χ^2 test yielded a P value of .006. No statistically significant differences were found when comparing the effect of dexamethasone in men and women. In addition, dexamethasone had no statistically significant effect on the incidence of permanent cranial nerve injuries. Finally, no adverse effect related to the administration of dexamethasone was observed.**

Conclusion: **Perioperative administration of dexamethasone is effective in minimizing the incidence of temporary cranial nerve injuries during CEA. (J Vasc Surg 2009;49:99-103.)**

The reported incidence of cranial nerve injury due to carotid endarterectomy (CEA) ranges from 7.6% to 50%,[1-6] depending on the methods used to detect such injuries. Although most cranial nerve deficits are transient, severe permanent dysfunction and even cranial nerve injury related deaths have been reported. Carotid artery stenting avoids this complication but not all patients can be treated by endovascular surgery. Current strategies for preventing cranial nerve injuries focus on a thorough understanding of the anatomical relationships, identification of nerves, careful handling of tissues, sharp dissection of the arterial wall, gentle retraction, and optimal hemostasis.[7] The potential for prevention or treatment of this common complication with pharmacological therapy has not yet been systematically evaluated.

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Competition of interest: none.

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The beneficial effects of dexamethasone (DEX) therapy in spinal cord injuries are well documented.[8-11] DEX has a pharmacological profile and a chemical structure similar to methylprednisolone (MPD), another glucocorticoid used for human therapy of spinal cord injury (SCI).[12,13] Like MPD, DEX therapy attenuates the expression of pro-inflammatory cytokines, such as TNF-α and IL-1β, that are increased at the injury site within the first few hours after SCI to regulate the subsequent cellular events.[14-16] These two cytokines also have an important function in the induction of inducible nitric oxide synthase leading to nitric oxide/peroxynitrite production and apoptotic cell death.[17] Indeed, apoptosis can be detected in the peri-lesion area after SCI. There is evidence that in addition to nitric oxide, either oxidative or nitrosative stress are involved in the secondary neuronal damage found in SCI.[18] Therefore, inhibition of free radical-mediated cell injury may be another beneficial effect of corticosteroid therapy. In the rat brain, DEX induces the expression of neurotrophic factors, such as nerve growth factor, basic fibroblast growth factor (FGF2), and brain-derived neurotrophic factors that are known to prevent cell death due to secondary injury.[19,20] Moreover, it has been demonstrated that FGF2 increases long-term survival of spinal motor neurons and improves respiratory function after experimental spinal cord injury.[21] Therefore,

the induction by DEX of neurotrophic factors could contribute to enhanced regenerative responses and functional recovery after SCI. In 1995, Lan Yao showed that DEX was able to facilitate the repair of the hypoglossal nerve in rats, but no studies proving its efficacy in human cranial nerve lesions have been published.[22] In 1999, we initiated a prospective randomized placebo-controlled trial to evaluate the efficacy of DEX in the prevention and treatment of carotid endarterectomy-related cranial nerve injuries.

MATERIAL AND METHODS

From March 1999 through April 2006, 1126 patients undergoing CEA because of high-grade carotid stenosis (≥70% luminal narrowing) were enrolled. Informed consent was obtained from all subjects. They were randomized by predetermined randomization tables into two groups and were treated by a single surgical and anesthesia team. Patients with restenosis or "hostile neck" (prior surgery, radiation) were excluded. The first group (A) included 586 patients (302 men and 284 women, aged 63-76). In addition to standard surgical and anesthesia management, all group A subjects received 8 mg of dexamethasone 1 hour before the operation, at 6 and 12 hours after the operation, every 12 hours on postoperative day #1, and once in the morning of postoperative day #2. The second group (B) included 540 control subjects (316 men and 224 women 62-76 years), who received the same standard pre- and postoperative therapy, including antibiotic prophylaxis and antiplatelet agents, but did not receive pre-treatment with DEX. In order to demonstrate a difference in cranial nerve injury of 4% between groups A and B with significance of 0.05 and power >0.8, we calculated a necessary sample size of 650 subjects in each group. This estimated sample size anticipated a loss to follow-up rate of 10%.

All patients were treated with deep cervical plexus block and eversion carotid endarterectomy with selective shunting. Three days after the operation a neurologist and an otorhinolaryngologist evaluated the presence of cranial nerve deficits by clinical examination and videolaryngoscopy. These physicians were blinded as to the group assignment of the patients. The nerve injuries were defined as temporary if the manifestations resolved within 12 months.

All patients (group A and group B) with nerve injuries received corticosteroid treatment (8 mg of dexamethasone daily) for 7 days following injury detection and were re-evaluated after 2 weeks, 30 days, and every 3 months for 1 year.

The χ^2 test was used for statistical analysis. Statistical significance was inferred for $P < .05$.

RESULTS

In Group A, 44% of the patients were asymptomatic, 29% had experienced one or more transient ischemic attacks (TIAs), 14% had non hemispheric symptoms, and 13% had suffered a major stroke. In Group B, 47.5% of the patients were asymptomatic, 27% had experienced one or more TIAs, 14% had non hemispheric symptoms, and 11.5% had suffered a major stroke (Table I).

Table I. Patients' demographics

Patients demographics	*Group A*	*Group B*	P *value*
Patients	586	540	
Gender			
Male	302	316	
Female	284	224	
Age (years)	63-76	62-76	
Hypertension	428 (73%)	410 (76%)	.2977
Diabetes mellitus	143 (24%)	115 (22%)	.2428
Smoking habit	174 (30%)	169 (31%)	.6036
Hyperlipidemia	227 (39%)	215 (40%)	.7574
History of MI	115 (20%)	102 (19%)	.8126
Symptoms			
TIA	170 (29%)	146 (27%)	.5030
nHS	82 (14%)	76 (14%)	.9689
Stroke	76 (13%)	62 (11.5%)	.5031
Asymptomatic	257 (44%)	257 (47.5%)	.2311

MI, Myocardial infarction; *TIA,* transient ischemic attack; *nHS,* non hemispheric symptoms (dizziness, syncope, headache, confusion).

In group A, 19 (3.2%) patients suffered cranial nerve injury, temporary in 2.3% and permanent in 0.9%. In group B, 37 (6.8%) patients experienced nerve dysfunction, temporary in 5.7% and permanent in 1.1% (Table II). For those with temporary lesions, recovery time took from 2 weeks to 10 months, with a mean time of 3.6 months. The difference in the incidence of cranial nerve injury in group A was statistically significantly less than that of group B ($P = .0081$) suggesting a beneficial role for dexamethasone. Of note is that the difference was seen only in the incidence of temporary injuries ($P = .006$) (Table III). There was no difference between the groups in the incidence of permanent injuries (0.9% vs 1.1%). Moreover, there were no statistically significant gender influences on the incidence of cranial nerve injury or on the effect of DEX treatment. No postoperative infections or other adverse effects related to administration of dexamethasone were observed.

The size and gender discrepancy between the two groups is due to loss of patients during follow-up (10%), to exclusion of patients due to perioperative stroke or death (2%), and to exclusions for other deaths within the follow-up period (0.9%) (Table IV).

DISCUSSION

The reported incidence of carotid endarterectomy-associated cranial nerve injury ranges from less than 7.6% to more than 50%, depending on whether the study was conducted prospectively or retrospectively and depending on the sensitivity of the methods employed for detecting cranial nerve injuries. Avoiding morbidity related to cranial nerve injuries has taken on even greater importance since carotid stenting now vies with endarterectomy for position as the default treatment for patients with severe carotid atherosclerosis.

Table II. Cranial and cervical nerve dysfunctions

	Group A		*Group B*	
	Temporary	*Permanent*	*Temporary*	*Permanent*
Laryngeal	1.2%	0.2	2.8%	0.4
Hypoglossal	0.8%	0.2	2.2%	0.1
Marginal mandibular	0.7%	0.3	1.1%	0.2
Transverse cervical	0.5	0.2	0.7	0.4
Spinal accessory	NR	NR	NR	NR
Glossopharyngeal	NR	NR	NR	NR

NR, Not recorded.

Table III. Cranial and cervical nerve injuries

	Group A	*Group B*	P *value*
Temporary	2.3%	5.7%	.006
Permanent	0.9	1.1	.8916
Total	3.2	6.8	.0081

The anatomy of the cranial and cervical nerves in the neck is both complex and variable. Furthermore, the ultrastructural characteristics of both the nerve fascicles and the epineural tissues determine their tolerance for mechanical and thermal trauma. The nerve trunks' elasticity and tensile strength, together with their ability to adapt to traction and deformation, depend on the fascicular tissues, while the epineurium has a protective role against compression forces.

Most cranial nerve injuries are caused by traction, compression, electrocautery, inadvertent clamping, ligatures, or partial to total transections. Such events can result in the full range of peripheral nerve injuries including:[23]

(1) Conduction loss without structural interruption.
(2) Axonal interruption with endoneural tube integrity.
(3) Axonal and endoneural tube disruption without epineural or perineural damage.
(4) Loss of continuity of the perineurium, distal Wallerian degeneration.
(5) Transection (loss of continuity of the epineurium, distal Wallerian degeneration).

Traction, compression, and electrocoagulation are mainly responsible for lesion types 1, 2, and 3, whereas ligature and complete transection are responsible for lesion types 4 and 5.

The perioperative inflammatory response related to operative trauma may play a role in modulating lesion types 1, 2, and 3 as well as those nerve injuries related to cervical plexus block and postoperative scarring. In view of the possibility that inflammation plays a role in perioperative cranial nerve dysfunction, we hypothesized that dexamethasone might help to prevent these complications. DEX has a long duration of action (T1/2 >200 minutes and duration of action between 36 and 54 hours) and also anti-inflammatory potency 30 times greater than that of cortisone.

Because several trials have established the effectiveness of DEX in improving outcomes in spinal cord injury patients, we thought it was reasonable to test our hypothesis in carotid endarterectomy-related cranial nerve injuries.

Furthermore, our hypothesis was supported by research performed at the University of Osaka in 1995.[22] In this study, rats with hypoglossal nerve injuries were treated with dexamethasone, which enhanced hypoglossal nerve nuclear levels of growth-associated protein (GAP)-43 messenger ribonucleic acid (mRNA) and facilitated regeneration. Since we could not measure the levels of GAP-43 mRNA in our patients, but were supported by reports of the effectiveness of this steroid in rats, we designed our study to test the clinical efficacy of DEX in ameliorating the clinical manifestations of operative trauma to the cranial nerves.

Our data reveal a statistically significantly lower incidence of clinically apparent cranial nerve injuries in patients treated with DEX. The beneficial effects of dexamethasone were noted only on the incidence of temporary nerve dysfunction. Dexamethasone treatment had no apparent effect on the incidence of permanent nerve dysfunction. This finding suggests that temporary nerve dysfunction may be caused by trauma-related local inflammation, while permanent deficits are related to loss of nerve integrity. Our study design does not permit evaluation of the effect of DEX on recovery time after nerve injury, since we felt it important to administer steroids postoperatively to patients in both groups A and B with postoperative clinical manifestations of nerve injury.

A number of complications can result from prolonged DEX therapy. These include fluid and electrolyte abnormalities, hypertension, hyperglycemia, increased susceptibility to infection, osteoporosis, myopathy, behavioral disturbances, cataracts, growth arrest, and the characteristic Cushing-like habitus of steroid overdose. However, a single dose, even a large one, is virtually free from harmful effects, and a short course of therapy (up to 1 week), in the absence of specific contraindications, is unlikely to be harmful. If the duration of therapy is increased beyond 1 week, there are time- and dose-related increases in the incidence of adverse effects.[24] In this regard, it should be pointed out that new strategies targeting multiple pro-

Table IV. Complication rates

	Group A	*Group B*	*Total*	P *value*
Perioperative stroke*	0.7%	0.9%	1.6%	.9020
Perioperative death*	0.2%	0.2%	0.4%	.9538
Perioperative respiratory complications	0.3%	0.4%	0.7%	.9347
Perioperative cardiac complications	0.8%	1.1%	1.9%	.8916
Neck hematoma and wound complications	0.7%	0.5%	1.2%	.7864
Other death* (≥30 postoperative day)	0.4%	0.5%	0.9%	.9270

*Patients excluded from the study.

inflammatory pathways (eg, low-dose dexamethasone plus etanercept or melatonin) are under investigation in experimental murine models of spinal cord trauma, in the attempt to minimize the risk of side effects experienced by patients treated with high-dose GC therapy. The results are providing evidence that the combined low-dose therapy may be effective and also safer than a single effector molecule for the management of SCI.[25]

In conclusion, our data demonstrate that pre- and postoperative administration of dexamethasone is effective in decreasing the incidence of temporary post-carotid endarterectomy cranial nerve dysfunction.

AUTHOR CONTRIBUTIONS

Conception and design: GR
Analysis and interpretation: DA
Data collection: GI, MF
Writing the article: GD, MC
Critical revision of the article: GR, DA
Final approval of the article: GR
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